38. (New) The oligonucleotide of claim 22 wherein said serum protein is human serum albumin.

B14

39. (New) The oligonucleotide of claim 26 wherein said serum protein is human serum albumin.

REMARKS

This responds to the final Office Action mailed on July 17, 2000, in connection with the above-identified patent application. Prior to the above amendments, Claims 1-36 were pending. Claims 3, 4, 24, and 32 are being canceled. New Claims 37-39 are being added. After the above amendments have been entered, Claims 1, 2, 5-23, 25-31, and 33-37 will be pending.

Independent Claims 1, 20, 27, 31, and 35 have been amended to recite covalently attaching an arylpropionic acid to an oligonucleotide. Support for the amendment can be found, for example, in the Specification at page 17, lines 9 and 28-30. Claims 2, 5, 6, 11, 13, 23, 25, 28, 30, 33, and 34 have been amended to be in conformance with the amendments to independent Claims 1, 20, 27, 31, and 35.

Claims 14-16 have been amended to clarify the antecedent basis for the term "linkages." Further, Claims 11 and 13 have been amended to provide appropriate antecedent basis for the claim terms, as suggested by the Examiner. The rejection of Claims 2-6 and 11-19 under 35 U.S.C. §112, second paragraph, is believed to be moot in view of the above amendments.

New Claims 37-39 have been added to more completely claim aspects of the present

Docket No: ISIS-3758 **PATENT**

In the claims:

Please amend the claims as follows:

1. (Amended) An [oligomeric compound] oligonucleotide [conjugated] covalently attached to a non-steroidal drug moiety [ligand] that interacts with a protein.

2. (Amended) The [oligomeric compound] oligonucleotide of claim 1 wherein said ligand binds to said protein.

3. (Amended) The [oligomeric compound] oligonucleotide of claim 1 wherein said ligand is a drug moiety.

4. (Amended) The [oligomeric compound] oligonucleotide of claim 3 wherein said drug moiety is aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

5. (Amended) The [oligomeric compound] oligonucleotide of claim 3 wherein said drug moiety is aspirin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, palmityl or carprofen.

6. (Amended) The [oligomeric compound] oligonucleotide of claim 3 wherein said drug moiety is ibuprofen.

7. (Amended) The [oligomeric compound] oligonucleotide of claim 1 wherein said protein is a cellular, serum or vascular protein.

8. (Amended) The [oligomeric compound] oligonucleotide of claim 7 wherein said protein is a serum protein.

9. (Amended) The [oligomeric compound] oligonucleotide of claim 8 having a K_d lower than 20 μM with at least one serum protein.

10. (Amended) The [oligomeric compound] oligonucleotide of claim 8 wherein said serum protein is albumin, an immunoglobulin, α-2-macroglobulin, α-1-glycoprotein or a lipoprotein.

11. (Amended) The [oligomeric compound] oligonucleotide of claim 1 further including a linking group attaching said ligand to said oligomeric compound.

12. (Amended) The [oligomeric compound] oligonucleotide of claim 11 wherein said linking group is 6-aminohexyloxy.

13. (Amended) The [oligomeric compound] oligonucleotide of claim 1 wherein said compound is an oligonucleotide comprising a plurality of nucleosides connected by covalent internucleoside linkages.

14. (Amended) The [oligomeric compound] oligonucleotide of claim 13 wherein said linkages are phosphodiester linkages.

15. (Amended) The [oligomeric compound] oligonucleotide of claim 13 wherein said linkages are phosphorothioate linkages.

16. (Amended) The [oligomeric compound] oligonucleotide of claim 13 wherein said linkages are non-phosphorus containing linkages.

17. (Amended) The [oligomeric compound] oligonucleotide of claim 13 wherein at least one of said nucleosides bears a 2'-substituent group.

18. (Amended) The [oligomeric compound] oligonucleotide of claim 17 wherein said 2'-substituent group is O-alkylalkoxy.

19. (Amended) The [oligomeric compound] oligonucleotide of claim 18 wherein said 2'-substituent group is methoxyethoxy.

SUB B5

20. (Amended) A method of increasing the concentration of an oligonucleotide in serum comprising the steps of:

(a) selecting a non-steroidal drug moiety that is known to bind to a serum protein;

(b) [conjugating] covalently attaching said drug moiety to said oligonucleotide to form a conjugated oligonucleotide; and

(c) adding said conjugated oligonucleotide to said serum.

SUB B6

27. (Amended) A method of increasing the capacity of serum for an oligonucleotide comprising the steps of:

(a) selecting a non-steroidal drug moiety that is known to bind to a serum protein;

(b) [conjugating] covalently attaching said drug moiety to said oligonucleotide to form a conjugated oligonucleotide; and

(c) adding said conjugated oligonucleotide to said serum.

SUB B11

31. (Amended) A method of increasing the binding of an oligonucleotide to a portion of the vascular system comprising the steps of:

(a) selecting a non-steroidal drug moiety that is known to bind to a protein that resides, in part, in the circulating serum and in part in a non-circulating portion of the vascular system;

(b) [conjugating] covalently attaching said drug moiety to said oligonucleotide to form a conjugated oligonucleotide; and

(c) adding said conjugated oligonucleotide to said vascular system.

35. (Amended) A method of promoting cellular uptake of an oligonucleotide in a cell comprising the steps of:

(a) selecting a protein that resides on the cellular membrane and extends, at least in part, on the external side of said membrane;

(b) selecting a drug moiety that is known to bind to said protein;

(c) [conjugating] covalently attaching said drug moiety to said oligonucleotide to form a conjugated oligonucleotide; and

(d) exposing said cell to said conjugated oligonucleotide.

REMARKS

Applicant is providing herewith a computer readable sequence listing, a paper copy of the sequence listing and a statement that the content of the paper and computer readable copies are the same and include no new matter, as required by 37 C.F.R. 1.821-1.825. Applicant respectfully requests that this sequence listing be entered into the specification.

Claims 1-36 are pending. Claims 1- 20, 27, 31, and 35 have been amended. No new matter has been added.

The title has been amended in accordance with the Examiner's suggestion.

Claims 1-3, 7, 8, 11-17, and 20-34 stand rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by Manoharan *et al.*, WO 93/07883. As the Office Action states, Manoharan discloses oligomeric compounds bound to ligands wherein the ligands may be steroids or cortisol moieties, which are steroidal. The amended claims specifically recite that the oligomeric compounds are bound to drug moieties are not steroidal, and therefore, the compounds disclosed in Manoharan are not within the scope of the present claims. (Support for the amendment can be found in the specification at, for example, page 10, lines 10-12). Accordingly, Applicant respectfully requests withdrawal of the rejection.

Claims 1-11 and 20-35 stand rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by Tomalia *et al.*, U.S. Pat. No. 5,714,166. Applicant respectfully traverses the rejection. The amended